The Effectiveness of Carboxyl as a Primary Ligating Group in Aryl–SO_2 N-Protected Amino Acids–Copper(II) Systems: Solution and Structural Investigation on the Cu(II)–*N*-Tosyl-L-leucinate System

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Abstract

The interaction between *N*-tosyl-L-leucine (tosyl = 4-toluenesulphonyl) and the copper(II) ion in aqueous–methanolic solution was examined. Two compounds of formula $Cu(tsleuO)_2 \cdot 4H_2O$ and $Na_2[Cu(tsleuNO)_2(H_2O)] \cdot 2H_2O \cdot CH_3OH$ [tsleuO = *N*-tosyl-L-leucinate(1–), tsleuNO = *N*-tosyl-L-leucinate(2–)] were isolated. For the second complex the crystal and molecular structure was also determined. The crystals were found to be monoclinic, space group $P2_1$ with $Z = 2$ in a unit cell of dimensions $a = 16.775(2)$, $b = 11.914(2)$, $c = 9.053(2)$ Å, $\beta = 100.54(1)°$. Full matrix least-squares refinement using 2900 independent reflections reached $R = 0.037$. The structure is built up of one $[Cu(tsleuNO)_2(H_2O)]$ dianion, two Na^+ cations, two lattice water molecules and one methanol solvate molecule. The coordination about the Cu atom is a distorted square-pyramidal arising from ligation of two *trans* amino acidate dianions acting as N,O ligands in the basal plane, and of one water oxygen in the axial position. The crystal packing is determined by Na^+–O interactions. By potentiometric and spectrophotometric measurements, the number and type of complex species and their cumulative formation constants were determined. The treatment of data confirmed, also in solution, the formation of the complexes separated in the solid state (stable, the first up to pH = 5 and the second above pH = 8). In addition, two complexes of formula [Cu(tsleuNO)] and $[Cu(tsleuO)(tsleuNO)]^-$ were found to prevail in the 5–8 pH range. The comparison of data with those of other aryl–SO_2 N-substituted α-amino acids indicates the same behaviour toward deprotonation of nitrogen and the effectiveness of carboxyl as a primary ligating group in preventing metal hydrolysis.

Introduction

The reaction pathway proposed to explain the anticipated amide nitrogen deprotonation in metal–oligoglycine systems involves first chelation of the metal ion through the terminal amino nitrogen and the neutral amide oxygen, with closure of a five-membered ring, thus preventing the metal hydrolysis [1–3].

On the contrary, for *N*-acetylglycine and *N*-acetyl-, *N*-benzoyl-, *N*-benzyloxycarbonyl-α-amino acids, which also possess a peptide group, the very abundant experimental results have invariably ruled out nitrogen deprotonation in the presence of metal ions, even in strongly alkaline media [2–6].

This behaviour is due to unfavourable structural conditions (e.g. closure of a seven-membered chelate ring) as well as to a weaker donor ability of the active sites (e.g. amidic and carboxylic oxygens) in *N*-acetylglycine-like molecules with respect to oligoglycine ones, which make the formation of the starting complex very unlikely. Thus the only active site which could act as anchor remains the carboxylate group, but the species formed normally have too low a stability to compete with metal hydrolysis in alkaline media.

Another class of investigated N-protected amino acids is represented by *N*-tosyl- and *N*-dansyl-α-amino acids*. These ligands undergo sulphonamide nitrogen deprotonation at pH values greater than 11 and with Cu(II) they should give rise to a 'biuret reaction' [2]; conversely they form stable carboxylates and N,O-chelate complexes upon titration of a mixture of Cu(II) and the ligand from acidic to basic pH, without metal hydrolysis, and the sulphonamide deprotonation occurs in the physiological pH range, as found for oligoglycines [7, 8]. These experimental data clearly conflict with the opinion that COO^- cannot act as an effective primary ligating group and some doubts on the suggested additional contribution of an $-SO_2-Cu$ interaction

*Abbreviations used throughout: tosyl = 4-toluenesulphonyl, dansyl = 5-dimethylaminonaphthalene-1-sulphonyl, tsgly = *N*-tosylglycine, tsglyO = *N*-tosylglycinate(1–), tsglyNO = *N*-tosylglycinate(2–), dnsgly = *N*-dansylglycine, tsvalO = *N*-tosyl-DL-valinate(1–).

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in the solution of carboxylate complexes require elucidation [3].

Now in order to collect more information to verify the generalization of the behaviour to most *N*-tosyl- and *N*-dansyl-α-amino acids and to suggest an explanation of the data, we report here the results of a spectroscopic and potentiometric solution study on the *N*-tosyl-L-leucine–copper(II) system. The study has been completed with the characterization of solid-state complexes. The crystal and molecular structure of disodium aquabis(*N*-tosyl-L-leucinato)-copper(II) dihydrate methanol solvate is reported.

Experimental

Reagents

N-Tosyl-L-leucine was recrystallized from a 1:1 methanol–water solution and concentrations of solutions used throughout were tested potentiometrically. Sodium hydroxide carbonate-free 0.1 and 0.01 mol/dm^3 NORMEX (C. Erba) was used as titrant. Copper(II) perchlorate hexahydrate was from Fluka and the concentration of the stock solution was determined with EDTA.

Potentiometric pH Measurements

Potentiometric measurements were performed at 25 ± 0.1 °C with the fully automatic Orion 960 Autochemistry system using a Ross 8102 SC combined electrode and a Centronics GLP II printer for recording e.m.f. and pH readings and titration curves. The electrode was calibrated by the method of Irving *et al.* [9] by using water/methanol = 4/1 (*v*/*v*) solutions. The ionic product K_w was obtained in the alkaline region of each calibration curve. No corrections were applied to pH values for the presence of a 25% volume of methanol.

All the experiments were carried out under a nitrogen atmosphere, determining the equivalent point by first-derivative technique [10], with constant mV increments in order to obtain almost 25 experimental points for each titration.

All the solutions were prepared by adding successively, to the measuring cell, a known volume of tsleuH aqueous solution and an exact volume of stock $Cu(ClO_4)_2 \cdot 6H_2O$ solution, 0.015 dm^3 of methanol (C. Erba) and a sufficient amount of doubly distilled water to reach a V_o volume of 0.060 dm^3 and the required quantity of $NaClO_4$ to adjust the ionic strength to 0.1.

The stability constants (β_{pqr}) which are defined by eqn. (1):

$$pL + qM + rH \longrightarrow L_pM_qH_r \quad (1)$$

$$\beta_{pqr} = [L_pM_qH_r]/[L]^p[M]^q[H]^r$$

were refined by a least-squares method by using the computer program SUPERQUAD [11]. During refinements $\sigma_E = 0.005$ (pH error) and $\sigma_v = 0.005$ (volume error) were employed. At first, ligand protonation constants were determined by refining several sets of potentiometric data; subsequently they were kept constant during the refinement of the stability constants of the complexes. All the calculations were performed on the Cray X-MP/12 computer of the Centro di Calcolo Elettronico.

Spectrophotometric Measurements

Absorption spectra were obtained on a Varian Cary 2300 spectrophotometer. The solutions, prepared with ionic strength 0.1 mol/dm^3 ($NaClO_4$) and methanol 25% (volume), were scanned by varying the NaOH amount at 25 °C using 10-cm cells.

Preparation of Complexes

$Cu(tsleuO)_2 \cdot 4H_2O$

On mixing 0.025 dm^3 of an aqueous solution of copper(II) perchlorate hexahydrate (10^{-2} mol/dm^3) and 0.025 dm^3 of water–methanol (5/1 *v*/*v*) solution of sodium *N*-tosyl-L-leucinate (2×10^{-2} mol/dm^3) a pale blue compound instantaneously precipitated. *Anal.* Found: C, 44.10; H, 6.06; N, 3.99; S, 8.99; H_2O, 10.30. Calc. for $C_{26}H_{44}CuN_2O_{12}S_2$: C, 44.32; H, 6.30; N, 3.98; S, 9.11; H_2O, 10.24%.

$Na_2[Cu(tsleuNO)_2(H_2O)] \cdot 2H_2O \cdot CH_3OH$

On dissolving 3×10^{-4} mol of the above cited complex in 0.030 dm^3 of methanol, adding NaOH until pH ≅ 10 and slowly evaporating the solution, a blue–green compound separated. *Anal.* Found: C, 41.80; H, 5.75; N, 3.61; S, 8.37; solvents, 11.11. Calc. for $C_{27}H_{44}CuN_2Na_2O_{12}S_2$: C, 42.52; H, 5.82; N, 3.68; S, 8.42; solvents, 10.68%.

Physical Measurements

The electronic, infrared and ESR spectra and thermogravimetric analyses in the solid state were recorded as in ref. 12.

Analyses

Sulphur, nitrogen, carbon and hydrogen were analysed with a C. Erba elemental analyser Model 1106 by Mr. G. Goldoni. The water and solvent contents were determined gravimetrically with thermal analyses performed at a rate of 5 °C min^{-1} with a Mettler TA3000 instrument.

Crystal Data

$C_{27}H_{44}CuN_2Na_2O_{12}S_2$: M = 762.3; monoclinic, a = 16.775(2), b = 11.914(2), c = 9.053(2) Å, β = 100.54(1)°, V = 1778.8 Å^3 (by least-squares refinement on diffractometer angles for 15 automatically centered reflections, λ = 1.54178 Å), space group $P2_1$ (C_2^2, No. 4), D_m = 1.42 g cm^{-3} (by flotation),

$Z = 2$, $D_c = 1.423$ g cm^{-3}; blue–green, air-stable prisms; crystal dimensions ~0.25 × 0.35 × 0.40 mm, μ(Cu Kα) = 25.5 cm^{-1}.

Systematic absences are compatible for either a non-centrosymmetric space group $P2_1$ or a centrosymmetric space group $P2_1/m$; the latter was ruled out by considering the presence of optically active L-α-amino acidate ions.

Data Collection and Processing

A Siemens AED diffractometer was used with ω–2θ scan method with ω scan width = 1.20° + 0.35 tan θ, scan speed 3–12 deg min^{-1}, Ni-filtered Cu Kα radiation Standards: 1 every 50 reflections (no changes; 3770 reflections measured ($2.0 \leqslant \theta \leqslant 60.0$; $\pm h, +k, +l$); 3567 unique (merging $R = 0.0154$) giving 2900 with $I > 3\sigma(I)$; absorption corrections were not applied.

Structure Analysis and Refinement

Conventional Patterson and Fourier techniques were used and full-matrix least-squares refinement [with $\Sigma w(|F_o| - |F_c|)^2$ being minimized] with all non-hydrogen atoms anisotropic and C-bonded hydrogens in calculated positions (C–H = 1.0 Å) with fixed B_{iso}; O-bonded hydrogens as were used fixed contributors in observed positions (from ΔF maps). The weighting scheme $w = 1/[\sigma^2(F_o) + 0.00403 F_o^2]$, with $\sigma(F_o)$ from counting statistics, gave analyses with satisfactory agreement. Final R and R_w values were 0.037 and 0.041. A final difference Fourier map was featureless, with no peaks higher than 0.27 e Å^{-3}. There was no evidence of secondary extinction. The enantiomeric model was chosen by assigning the known *S*-configuration, according to the Cahn–Ingold notation, to the optically active centre of the *N*-tosyl-L-leucinate anion. Complex neutral atom (except for Na^+) scattering factors [13] were used throughout. Major calculations were carried out on a VAX 11/750 computer by using SHELX 76 system of programs [14] and the ORTEP [15] for drawing. Final fractional coordinates for non-hydrogen atoms are given in Table I.

TABLE I. Final Positional Parameters

Atom	*x/a*	*y/b*	*z/c*
Cu	0.12910(4)	0.25	0.42074(9)
O(1)	0.1079(2)	0.2304(3)	0.6251(4)
C(1)	0.1297(3)	0.1350(5)	0.6873(7)
O(2)	0.1161(3)	0.1080(4)	0.8114(5)
C(2)	0.1736(4)	0.0540(5)	0.6001(6)
C(3)	0.2626(4)	0.0429(5)	0.6740(7)
C(4)	0.3158(4)	0.1472(7)	0.670(1)
C(5)	0.3061(5)	0.2322(8)	0.792(1)
C(6)	0.4031(5)	0.115(1)	0.691(1)
N(1)	0.1594(3)	0.0908(4)	0.4421(5)
S(1)	0.16266(7)	−0.0030(1)	0.3206(2)
O(3)	0.1144(2)	0.0345(3)	0.1815(5)
O(4)	0.1450(2)	−0.1115(3)	0.3714(5)
C(7)	0.2631(3)	−0.0107(5)	0.2846(6)
C(8)	0.3086(4)	−0.1061(5)	0.3209(8)
C(9)	0.3873(4)	−0.1137(7)	0.2920(9)
C(10)	0.4210(4)	−0.0247(7)	0.2269(9)
C(11)	0.3754(5)	0.0697(7)	0.193(1)
C(12)	0.2956(4)	0.0786(7)	0.218(1)
C(13)	0.5053(5)	−0.032(1)	0.193(1)
O(5)	0.1452(2)	0.2747(3)	0.2116(4)
C(14)	0.1708(3)	0.3733(5)	0.1846(7)
O(6)	0.1711(3)	0.4103(4)	0.0580(5)
C(15)	0.2014(3)	0.4434(5)	0.3233(6)
C(16)	0.2899(4)	0.4106(6)	0.3904(8)
C(17)	0.3526(4)	0.4406(7)	0.295(1)
C(18)	0.3677(6)	0.5645(9)	0.297(1)
C(19)	0.4324(5)	0.380(1)	0.356(1)
N(2)	0.1478(3)	0.4167(4)	0.4305(6)
S(2)	0.10899(8)	0.5161(1)	0.4993(2)
O(7)	0.0502(3)	0.4785(4)	0.5841(6)
O(8)	0.0805(3)	0.6059(4)	0.3893(5)
C(20)	0.1889(4)	0.5826(5)	0.6271(7)
C(21)	0.2172(5)	0.5340(6)	0.7629(8)
C(22)	0.2824(5)	0.5808(7)	0.8591(9)
C(23)	0.3217(5)	0.6755(7)	0.8171(9)
C(24)	0.2921(4)	0.7229(6)	0.6785(8)
C(25)	0.2263(4)	0.6772(6)	0.5841(8)
C(26)	0.3914(6)	0.729(1)	0.919(1)
Ow(1)	−0.0133(3)	0.2474(5)	0.3560(5)
Na(1)	0.0649(2)	0.1721(2)	0.0147(3)
Na(2)	0.0193(1)	0.8036(2)	0.3746(3)
Ow(2)	0.0169(3)	0.3396(4)	0.8889(5)
Ow(3)	0.0626(5)	0.6029(7)	0.0664(9)
Ome	0.0881(4)	0.8842(5)	0.8764(6)
Cme	0.1607(7)	0.839(1)	0.939(1)

Results and Discussion

Solid State Complexes

The pale blue Cu(tsleuO)$_2$·4H$_2$O shows electronic and ESR data (Table II) which are consistent with a distorted octahedral coordination geometry with the CuO_6 chromophore as found in the structurally known monomeric [Cu(tsvalO)$_2$(H$_2$O)$_2$(CH$_3$OH)$_2$] complex [16]. In the infrared spectrum the frequencies of the SO_2 group, very close to those of the above cited *N*-tosyl-DL-valinate complex, similarly suggest that the tsleuO anion acts as a simple carboxylate ligand, excluding any significant sulphonyl oxygen–metal interaction, which should require polymeric geometries [17a, 18, 19].

Description of the Structure of Na$_2$[Cu(tsleuNO)$_2$(H$_2$O)]·2H$_2$O·CH$_3$OH

The structure is built up of one [Cu(tsleuNO)$_2$(H$_2$O)]$^{2-}$ dianion, two Na^+ cations interacting with O atoms, two lattice water molecules and one methanol solvate molecule. Selected bond distances

TABLE II. Room Temperature (298 K) ESR, Electronic and Infrared Data for Solid Copper(II)–*N*-Tosyl-L-leucinate Complexes

	$Cu(tsleuO)_2 \cdot 4H_2O$ [a]	$Na_2[Cu(tsleuNO)_2(H_2O)] \cdot 2H_2O \cdot CH_3OH$
$g_\parallel$	2.36	2.27
$g_\perp$	2.09	2.07
$\langle g \rangle$	2.18	2.14
d–d transition ν (cm^{-1})	12500sh, 13200	14900
ν(OH) (cm^{-1})	3580, 3450mb	3580, 3530, 3470ms
ν(NH) (cm^{-1})	3280m	
$\nu(OCO)_{asym}$ (cm^{-1})	1570vs	1600vs
$\nu(OCO)_{sym}$ (cm^{-1})	1410s	1400s
$\nu(SO_2)_{asym}$ (cm^{-1})	1320, 1305vs	1250vs
$\nu(SO_2)_{sym}$ (cm^{-1})	1150vs	1140vs
ν(SN) (cm^{-1})	930m	965, 990s

[a] $A_\parallel = 203 \times 10^{-4}$ cm^{-1}.

TABLE III. Selected Bond Distances (Å) and Bond Angles (deg)

Cu–O(1)	1.961(3)	Cu–O(5)	1.983(4)
Cu–N(1)	1.964(4)	Cu–N(2)	2.011(4)
Cu–Ow(1)	2.353(4)		
C(1)–O(1)	1.291(6)	C(14)–O(5)	1.290(6)
C(1)–O(2)	1.230(7)	C(14)–O(6)	1.228(7)
C(2)–N(1)	1.473(6)	C(15)–N(2)	1.472(7)
N(1)–S(1)	1.576(4)	N(2)–S(2)	1.537(5)
S(1)–O(3)	1.438(4)	S(2)–O(7)	1.428(4)
S(1)–O(4)	1.421(4)	S(2)–O(8)	1.480(4)
S(1)–C(7)	1.777(5)	S(2)–C(20)	1.788(6)
O(1)–Cu–N(1)	83.1(2)	O(1)–Cu–O(5)	176.9(2)
O(1)–Cu–N(2)	97.5(2)	O(1)–Cu–Ow(1)	83.2(2)
N(1)–Cu–O(5)	99.2(2)	N(1)–Cu–N(2)	156.1(2)
N(1)–Cu–Ow(1)	104.1(2)	O(5)–Cu–N(2)	81.2(2)
O(5)–Cu–Ow(1)	94.2(2)	N(2)–Cu–Ow(1)	99.6(2)

and bond angles are reported in Table III, with atoms numbered as in Fig. 1.

The Cu atom displays a distorted square-pyramidal penta-coordination arising from ligation of two *trans* $tsleuNO^{2-}$ anions acting as bidentate ligands in the equatorial plane through one carboxylate oxygen and the amide nitrogen, and of one water molecule in the axial position. The basal coordination plane is tetrahedrally distorted with atomic deviations ranging from −0.23 to +0.23 Å; the metal atom is displaced 0.184 Å from the plane toward the apical donor atom, whose bond direction deviates 6.2° from the normal to the basal plane. The Cu–O and Cu–N equatorial bond distances compare well with those reported for other tosyl N-substituted α-amino acidate dianions acting as bidentate ligands [7, 17a, 20], and the extent of distortions from ideal square-pyramidal geometry is in a range commonly reported for many small peptide or amino acid copper(II) complexes [3, 21, 22].

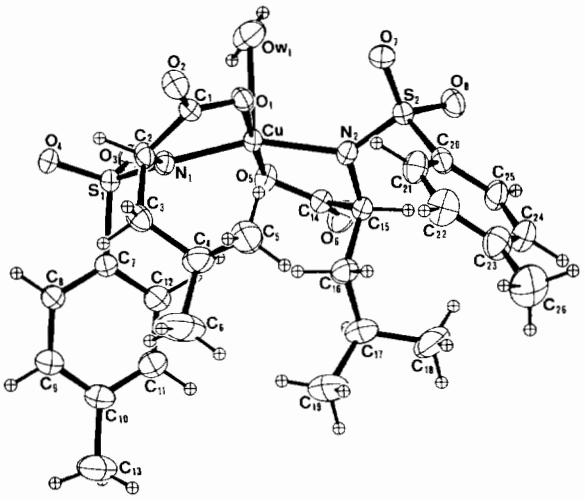

Fig. 1. ORTEP view of the $[Cu(tsleuNO)_2(H_2O)]$ complex dianion showing the atom numbering and thermal motion ellipsoids (40%). The spheres corresponding to the hydrogen atoms are on an arbitrary scale.

The largest difference between the dimensions of the two crystallographically independent $tsleuNO^{2-}$ ligands involves the conformation of the five-membered chelate rings, with torsion angles at the C–C bond of −17.0° and −36.7°, respectively. Bond distances and bond angles are normal and consistent with those previously observed in other *N*-tosyl-α-amino acidate dianions [7, 17a, 20]. It is of interest to note that within the carboxylate groups the C–O bond distances for coordinated O atoms (average 1.290(6) Å) are significantly longer than those involving uncoordinated oxygens (mean value 1.229(7) Å). A further relevant feature is the stronger double bond character of the N–S bond (1.537(5) and 1.576(4) Å) with respect to undeprotonated *N*-tosyl derivatives, whose corresponding N–S bond distances were found to be in the 1.584–1.621 Å range [17a, 18, 20]. An opposite, but weaker,

lengthening of the S–C bond distance (1.777(5) and 1.788(6) Å, respectively) was observed.

The sodium ions have two different nearest neighbours. The first is penta-coordinated in an irregular geometry by two carboxylic, one sulphonic and two water oxygens, with Na–O bond distances in the 2.280(4)–2.367(4) Å range. The coordination about the second Na^+ ion is a distorted octahedral with six O atoms (one carboxylic, three sulphonic and two water oxygens) and interatomic separations ranging from 2.306(4) to 2.563(5) Å.

The crystal packing is mainly determined by the interactions of the sodium ions, which link complex anions and water molecules in an infinite tri-dimensional network. Further contributions to the crystal packing forces come from hydrogen bonds which involve water molecules, carboxylic or sulphonic oxygens, and the methanol solvate molecule.

Spectroscopic Properties

The electronic spectrum presents a broad maximum at slightly lower energy (Table II) with respect to $K_2[Cu(tsglyNO)_2]$ (15 150 cm^{-1}), as expected because of the shorter $Cu–O_{ax}$ distance in the tsleu complex (2.353(4) *versus* 2.717(5) Å in the tsgly complex [17a]), while ESR parameters of the tsleu complex are shifted toward a greater $g_{\parallel}$ value as a consequence of the increasing axial ligand field. The more relevant IR bands are reported in Table II and assigned by comparison with the spectra of other deprotonated *N*-tosyl-α-amino acidate–copper(II) complexes.

Solution Behaviour

N-Tosyl-L-leucine

The protonation behaviour, investigated in aqueous and aqueous–methanol (CH_3OH = 25% *v/v*) (Fig. 2 and Table IV) solutions from potentiometric and spectrophotometric analyses, is represented by the following equilibria:

$$CH_3C_6H_4SO_2\bar{N}CH(CH_2CH(CH_3)_2)COO^- + H^+ \overset{\beta_{101}}{\rightleftharpoons} CH_3C_6H_4SO_2NHCH(CH_2CH(CH_3)_2)COO^- \quad (2)$$

$$CH_3C_6H_4SO_2\bar{N}CH(CH_2CH(CH_3)_2)COO^- + 2H^+ \overset{\beta_{102}}{\rightleftharpoons} CH_3C_6H_4SO_2NHCH(CH_2CH(CH_3)_2)COOH \quad (3)$$

The value of $\log K_2^H$ in H_2O (Table IV) is very close to other *N*-tosyl-α-amino acids (*N*-tosylglycine = 3.5 [17b], *N*-tosyl-α-alanine = 3.43(2) [23] because the equilibrium involving the carboxylate group is almost unaffected by the complexity of the alkyl chain. On the contrary, the differences observed in $\log K_1$ (*N*-tosylglycine = 11.6 [17b], *N*-tosyl-α-alanine = 11.80(1) [23]) parallel the slight increasingly inductive effect of alkyl chains, leading to a decrease of sulphonamide group acidic character. Furthermore, owing to the negative charge of the ionized carboxyl, which is also delocalized on the sulphonamide group, $\log K_1^H$ for all these ligands is markedly greater than that of parent 4-toluenesulphonamide ($\log K$ = 10.17 [24]).

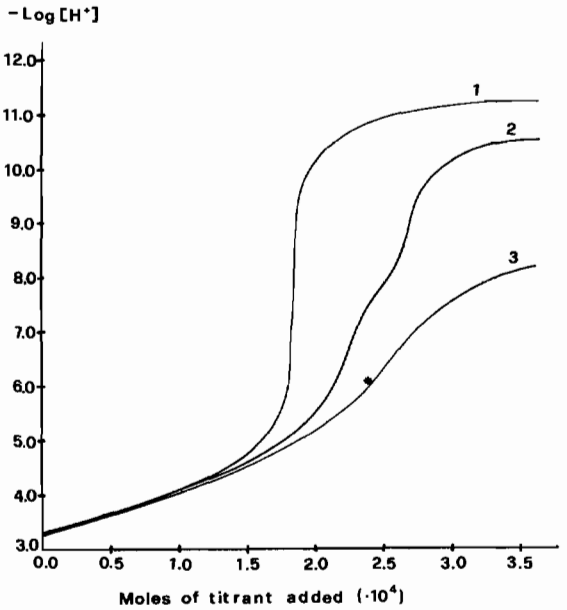

Fig. 2. Titration curves of pH as a function of the moles of NaOH added. $m_{tsleu} = 1.8 \times 10^{-4}$; (1) $m_{Cu} = 0.0$, (2) $m_{Cu} = 3.96 \times 10^{-5}$, (3) $m_{Cu} = 7.8 \times 10^{-5}$. *m* = number of moles. * After this point copper(II) hydroxide precipitation takes place.

TABLE IV. Overall Stability Constants of Cu(II)–*N*-Tosyl-L-leucinate Complexes. I = 0.1 M ($NaClO_4$) at 25 °C

		H_2O	CH_3OH (25% *v/v*)
tsleuH	$\log \beta_{101}$	12.00(2)	12.33(2)
$tsleuH_2$	$\log \beta_{102}$	15.47(2)	16.34(2)
	$\log K_2^H$	3.47(1)	4.01(1)
[Cu(tsleuNO)]	$\log \beta_{110}$		9.06(4)
$[Cu(tsleuNO)_2]^{2-}$	$\log \beta_{210}$		16.80(2)
[Cu(tsleuO)(tsleuNO)]$^-$	$\log \beta_{211}$		24.51(1)
$[Cu(tsleuO)_2]$	$\log \beta_{212}$		29.53(2)

The Cu(II)–N-tosyl-L-leucine system

The pH-metric titrations of the Cu(II)–tsleu system, both in aqueous and mixed solvent solutions, were performed at 1:2, 1:4 and 1:8 metal-to-ligand molar ratios. In aqueous media the separation of copper(II) hydroxide at pH > 6 prevents the investi-

gation of the system. The same holds for mixed solvents in metal-to-ligand molar ratios of 1:2. The titration curves reported in Fig. 2 are quite superimposable for the ligand and ligand–metal systems up to pH = 4, suggesting that no complex formation takes place before almost complete carboxylate ionization. Furthermore, two equivalent points are clearly observed. The amount of NaOH necessary to reach the first and the second point depends on the metal-to-ligand molar ratio, according to equations:

$$m_{NaOH} = m_{tsleu} + m_{Cu} \quad (4)$$

$$m_{NaOH} = m_{tsleu} + 2m_{Cu} \quad (5)$$

where m is the number of moles.

Solution spectrophotometric measurements (Table V) were performed with the aim of identifying the formation of different complexes at increasing pH values and of defining the ligand bonding mode by comparison with the solid complexes. The displacement toward higher energy with respect to the $Cu(H_2O)_6^{2+}$ ion which occurs at the first equivalent point is compatible with both [Cu(tsleuNO)] and $[Cu(tsleuO)(tsleuNO)]^-$ complexes which correspond to the same $CuNO_5$ chromophore. At the second equivalent point the intensely blue solution shows a maximum absorption band near to that of solid $Na_2[Cu(tsleuNO)_2(H_2O)]\cdot 2H_2O\cdot CH_3OH$, which separates from the same solution, so the presence of equatorial CuN_2O_2 chromophore is also assumed for the solution species.

TABLE V. Position of Absorption Bands (λ_{max} in cm^{-1}) of the Solution Copper(II)–*N*-Tosyl-L-leucinate Complexes; $c_L = 3.3 \times 10^{-3}$ M, $c_{Cu^{2+}} = 8.25 \times 10^{-4}$ M

[NaOH]/[tsleu]	λ_{max} (cm^{-1})
0	12400
1	13200
1.25	13400
1.5	15600
2	15600

The finding of only two equivalent points and the invariance in maximum position also in strong alkaline solution excludes the formation of a tris-chelate.

In the calculation process, in addition to the stability constants of the above complexes, the formation of a bis-carboxylate species $[Cu(tsleuO)_2]$ was also taken in account, improving the data fit. Furthermore, the same complex was confirmed by considering tsleu as a monoprotic ligand, according to the reaction:

$$Cu^{2+} + 2tsleuO^- \overset{\beta'_{210}}{\rightleftharpoons} [Cu(tsleuO)_2]$$

where the calculated log β'_{210} value was 4.87(2).

Finally, the evaluation of data excluded the presence of mixed-hydroxy complexes in the whole pH range investigated, as well as the species [Cu(tsleuO)] even at the lowest ligand-to-metal molar ratio.

The refined overall stability constants are collected in Table IV and the species distribution curve is reported in Fig. 3.

The comparison of data for solution and solid systems indicated that the coordination behaviour of tsleu is quite similar to that of tsgly and dnsgly, and seems common for this class of molecules. The differences in log β of analagous species, reflecting a lower coordination ability of tsleu with respect to tsgly, may be ascribed to steric factors which, particularly for dnsgly, favour the binding of only one ligand molecule [8, 17b, 19].

In spite of its moderate coordination ability in mixed solvent, at a ligand-to-metal molar ratio greater than 4, the substitution of carboxylic hydrogen by the metal ion in acidic regions also takes place for tsleu ($\beta'_{210} > K_2^H$); a significant percentage (~20% of the total Cu(II) ion) of $[Cu(tsleuO)_2]$ is formed, lowering the concentration of free metal ion and thus preventing its hydrolysis. For the formation of $[Cu(tsleuO)_2]$ solution species, the stabilizing contribution of a metal–sulphonyl oxygen interaction

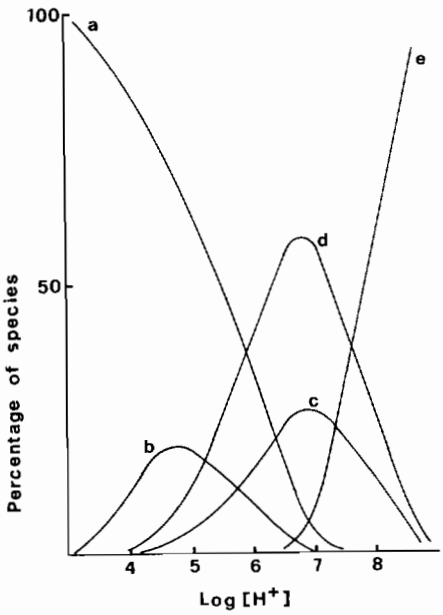

Fig. 3. Species distribution curves for the complexes at 4:1 ligand-to-metal molar ratio. $c_{Cu} = 5 \times 10^{-4}$ mol/dm^3: a = $[Cu^{2+}]$; b = $[Cu(tsleuO)_2]$; c = [Cu(tsleuNO)]; d = $[Cu(tsleuO)(tsleuNO)]^-$; e = $[Cu(tsleuNO)_2]^{2-}$.

may be excluded as the structural data show that $-SO_2$ involvement leads to polynuclear species [16, 18, 19] not recognized in solution.

At the same time, upon complexation, the negative charge on the carboxyl group is neutralized and the Cu–O bond of the complex, stronger than the O–H bond of the free ligand, now enhances the acidic character of the N–H bond which becomes greater than in the parent 4-toluenesulphonamide. Thus with the aid of simultaneous closure of the penta-atomic chelate ring, the deprotonation reaction begins at pH > 6, far in advance with respect to free tsleu.

Our conclusions indicate that the solution carboxylate complexes formed by *N*-tosyl- and *N*-dansyl-α-amino acids have quite comparable stabilities, dependent on the complexity of the ligand molecules. The effectiveness as a primary ligating group of a carboxyl group, although less than that of an amino group in oligoglycines, is thus demonstrated. This capability, together with the cooperative electrophilic effect of the $-SO_2$ group on the amide nitrogen, causes a much greater reduction in the deprotonation pH than occurs in peptides.

In *N*-acetylglycine-like molecules, although solution carboxylate species are formed [5, 6], they are unable to enhance sufficiently the acidic character of the peptide nitrogen ($pK_a \approx 15$), so that metal hydrolysis prevails.

Supplementary Material

A list of anisotropic temperature factors, H-atom parameters, interatomic distances and angles, intermolecular contacts, selected least-squares planes, observed and calculated structure factors (24 pages) are available from the authors on request.

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